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Enhanced decision support for policy makers using a web interface to health-economic models—Illustrated with a cost-effectiveness analysis of nation-wide infant vaccination with the 7-valent pneumococcal conjugate vaccine in the Netherlands

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Abstract

We have developed a web-based user-interface (web interface) to enhance the usefulness of health-economic evaluations to support decision making (<http://pcv.healththeconomics.nl>). It allows the user to interact with a health-economic model to evaluate predefined and customized scenarios and perform sensitivity analysis. To explore its usefulness, it was applied to an evaluation of cost-effectiveness of nation-wide infant vaccination with the 7-valent pneumococcal conjugate vaccine (PCV7), that was used to support a policy decision on the inclusion of PCV7 in the national vaccination program (NVP) of the Netherlands. We used a decision-tree analytic model to project the impact of infant vaccination with four doses of PCV7 on an annual cohort of infants born in the Netherlands. The base-case analysis includes the beneficial effects on unvaccinated individuals (herd protection). Additional scenarios varying the number of doses, discount rate for effects and the number of serotypes in the vaccine were evaluated and can be analysed on the web. Our model projects a base-case incremental cost-effectiveness ratio (iCER) of €14,000 (95% uncertainty interval (UI): 9,800–20,200) per quality adjusted life year (QALY) or €15,600 (95% UI: 11,100–23,900) per life year gained (LYG).

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Keywords: Pneumococcal conjugate vaccine PCV; Web interface for policy decision support; Cost effectiveness

1. Introduction

Decision makers in various countries increasingly use economic evaluation to support decisions on the inclusion of new vaccines in their NVPs. For example, Welte et al. recently

presented an overview on the role of health-economics in decision making concerning the introduction of meningococcal group C conjugate vaccines in NVPs [1]. The type of analysis underlying such economic evaluation generally employs some form of modeling to simulate the costs and effects of a vaccination program. In this study we focus on further enhancing the flexibility of applying such models and the transparency of their results. Our approach aims to increase the applicability of these evaluations to support policy decisions by providing a web interface for economic models. This web interface provides the flexibility to evaluate

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predefined and customized scenarios. In addition, it allows the user to perform sensitivity analysis and generate various graphs, such as cost-effectiveness acceptability curves and scatter plots. By observing the impact of changes in model parameters, the user is provided with additional insights into the model, its limitations and the intrinsic uncertainty of the model outcome.

As an illustration we will present the results of a study that has recently been used to support a recommendation of the Health Council to the Ministry of Health on nationwide vaccination of infants with PCV7 (Prenar[®]/Prevenar[®], Wyeth) in the Netherlands. In particular, inclusion of PCV7 against *Streptococcus pneumoniae* in the NVP of the Netherlands was recommended (and is now implemented), also based on our cost-effectiveness estimates [2].

Pneumococcal infections in infants present an important cause of invasive disease such as meningitis and bacteremia, and non-invasive disease such as pneumonia and otitis media. Invasive Pneumococcal Disease (IPD) is associated with high mortality rates [3,4] and may cause severe lifelong complications [5,6]. Non-invasive pneumococcal disease causes a high burden to society due to the high incidence of infection-related disease, such as otitis media and pneumonia. In Western Europe, it is estimated that every child experiences one or more episodes of otitis media before the age of 2 years [7,8]. A number of studies have assessed the potential economical impact of mass infant vaccination with PCV7 (Prenar; Wyeth) [9–12], since the first published clinical trial showed the high efficacy of this vaccine in the prevention of IPD [13] (see also McIntosh [14] for a recent review). Additionally, ongoing research has provided important new data. For example, recent evidence indicates that with less than four doses of the vaccine a sufficient level of immunological protection might also be attained [15]. Also, protective effects of infant vaccination on unvaccinated age groups (herd protection), have been reported by Whitney et al. [16]. In a health-economic analysis, Melegaro and Edmunds have shown a very substantial effect of the inclusion of herd protection on the iCER in England and Wales, reducing it more than 10 fold [12].

For the Netherlands an economic evaluation was published previously by Bos et al. based on research during 2000–2001 [17]. Their model estimated the impact and cost-effectiveness of nation-wide infant vaccination with PCV7 at the age of 2, 3, 4 and 12 months. In this paper we present the updated results obtained with this model with recent epidemiological and cost data, including the effects of herd protection, alternative dosage schedules and alternative polyvalent vaccines. All presented scenario- and sensitivity analyses were performed with the web interface that is publicly accessible at <http://pcv.healthconomics.nl>. In the discussion, we will further address the role web-based interaction with economic models could play to support decision making.

2. Methods

2.1. Model

In this section we present a brief description of the original study by Bos et al. [17] that was used as the basis for this evaluation. It was updated to include recent epidemiologic data and health care unit costs. Bos et al. used a decision-tree analytic model to project the impact of infant vaccination with four doses of PCV7 on the incidence of pneumococcal infections in infants and children up to and including 9 years of age from a societal perspective. The cost per dose of vaccination including administration costs was assumed to be €45.20. The decision tree differentiated between the complications of meningitis, bacteremia, pneumonia and otitis media. Lifetime costs, financial benefits and health gains were estimated for an annual cohort of ~200,000 infants (source: Central Bureau of Statistics) born in the Netherlands in 2001. Both health effects and costs were discounted at a rate of 4%. The analytic time frame of the study was 10 years, corresponding to the assumed period of protection of the vaccine. To assess the potential serotype coverage of the vaccine against disease-causing serotypes and the incidence of IPD (pneumococcal meningitis and pneumococcal bacteremia) data from the Netherlands Reference Laboratory for Bacterial Meningitis (NRBM) for the years 1996–2001 was used [18]. The age specific incidences of pneumonia and otitis media were estimated using data from the Integrated Primary Care Information Project (IPCI) [19] for the years 1997–2000. The length of hospital stay (LOS) was estimated using data from PRISMANT Health Care for the years 1996–2001 [20]. QALYs and corresponding losses in quality of life due to neurological and physical sequelae, hearing impairments and invasive pneumonia was considered using EuroQol assessments. An in depth description of the model can be found in the original paper [17].

2.2. Updating the model

In particular, the average number of cases of IPD per year was updated with data on the years 2001–2004 from the Netherlands Reference Laboratory for Bacterial Meningitis (NRBM) [21]. This data is shown in Table 1, corrected for underreporting (the percentages of reported bacteremia and meningitis cases in the Netherlands were assumed to be 40% and 80%, respectively [22]).

Also shown in Table 1, are the average number of cases of pneumonia and the average number of episodes of otitis media per year in the Netherlands as derived from the IPCI database (based on general practitioner (GP) patient records), irrespective of causative agent [19]. The number of episodes of otitis media was adjusted to account for the percentage of registered cases in the IPCI database (cases treated by a GP), assumed to be 30% [23]. Tables 2 and 3 show the clinical and resource use parameters used in the model. Unit costs

Table 1

The average number of cases per year in the Netherlands of pneumococcal meningitis and pneumococcal bacteremia over the years 2001–2004 per age [21]

Age	Meningitis	Bacteremia	Pneumonia	Otitis media
0–4 months	18	38	3400	103,067
5–11 months	45	48	3740	183,867
1 year	22	51	1960	155,200
2 years	6	31	3840	100,867
3 years	5	19	4740	114,600
4 years	4	9	3380	81,133
5 years	4	11	4020	71,667
6 years	2	6	2900	44,867
7 years	3	8	2580	27,067
8 years	2	4	1380	19,800
9 years	1	4	1380	19,800

Also shown are the average number of cases of clinical pneumonia and episodes of otitis media per year in the Netherlands (irrespective of causative agent) over the years 1996–2001 [19]. Pneumococcal meningitis, pneumococcal bacteremia and otitis media were corrected for underreporting.

were updated to adhere to the most recent version of the Dutch guidelines on costing in pharmacoeconomic research [24]. Costs were measured in € using price levels of the year 2004. The cost per dose of vaccination including administration costs was assumed at €50 (Personal communication with the Dutch Ministry of Health). Economic evaluation was based on a cohort consisting of 193,789 infants born in the Netherlands in 2004 with an average life expectancy for newborns of 79 years (source: Central Bureau of Statistics). For the threshold analysis on the vaccine cost per dose, the only published – but still informal – Dutch threshold for cost-effectiveness at €20,000 per LYG or QALY [25] was used.

The model used by Bos et al. [17] was further extended by the inclusion of an estimate of the effects of herd protection using the estimated decline in the incidence of IPD for all serotypes in unvaccinated age groups published by Whitney et al. [16] shown in Table 4.

Herd protection was assumed to affect only the number of cases with invasive manifestations of pneumococcal disease (bacteremia, meningitis). Possible reductions in cases of otitis media, pneumonia and meningitis sequelae were not taken into account. We assumed the herd protection effects for the duration of 1 year, to be consistent with the basis of our analysis, i.e. one annual cohort of newborn infants. The average number of cases of pneumococcal meningitis and pneumococcal bacteremia per year in the Netherlands in these unvaccinated age groups is shown in Table 4. Of these cases, 50% of total bacteremia cases were assumed to cause morbidity, whereas the other 50% was assumed not to be harmful in nature (Personal communication Dr. L. Spanjaard, Netherlands Reference Laboratory Meningitis, RIVM/AMC). The mortality rate for serious cases of pneumococcal bacteremia and meningitis among adults in the Netherlands was assumed to be 25.9% [26] and 30.4%, respectively [27]. Indirect costs due to mortality were calculated using the friction cost method with a friction period of 154 days [24]. A vaccination schedule of four doses of PCV7 administered at the age of 2, 3, 4 and 12 months was used. Efficacy was assumed being absent before the age of

5 months. Based on the results of Black et al. [13], efficacy was assumed to be 85.7% at the ages of 5–11 months and 93.9% at the ages of 12 months to 9 years. Vaccine effectiveness was assumed to decline 3% per year starting 5 years after the last dosage [11]. Vaccine effectiveness against IPD was calculated by multiplying the efficacy of the vaccine with the serotype coverage (the proportion of IPD causing isolates with serotypes covered by the vaccine in the Netherlands [21] for the age group 0–9 years). The effectiveness of the vaccine against pneumonia and otitis media in children was assumed to be 6% [28] and 6.4% [13], respectively (Tables 1–4).

2.3. Web interface

This section describes the web interface that was used to perform the scenario and sensitivity analyses. It can be linked to health-economic models of various types (decision analytical, Markov, discrete event simulation) designed with commonly used software packages. Linking requires some non-structural changes to the model. The web interface provides the user with an overview of relevant input parameters. The values of the input parameters can be changed within their predefined constraints. The user can evaluate a predefined or customized scenarios and is provided with a numeric table of corresponding outcome parameters. Also, three types of sensitivity analysis are available: univariate analysis, bivariate analysis and multivariate (probabilistic) analysis. Results of a univariate and bivariate sensitivity analysis are presented in a two-dimensional line plot and three-dimensional surface plot, respectively (the default domain is –25% to +25% of the base-case parameter values). In the multivariate (probabilistic) analysis random values from user-specified distributions are drawn in a Monte Carlo simulation [32–34]. An appropriate default distribution type is specified for each input parameter (normal, lognormal, standard beta, uniform, triangle or gamma distribution). If a distribution type other than the default is selected, the user should be aware that not every distribution type is always appropriate. The distribution parameters are calculated from the mean and standard error. Box 1 shows how the standard

Table 2

Unit costs (in €; price-levels: 2004), clinical and resource use parameters

Parameter description	Value
Direct cost per case of uncomplicated meningitis or bacteremia [24]	€7,431
Direct cost per case of complicated meningitis [24]	€26,787
Mean direct cost of uncomplicated and complicated otitis media per episode [24]	€21
Direct cost per case of mild pneumonia [24]	€97
Direct cost per case of uncomplicated pneumonia [24]	€161
Direct cost per case of complicated pneumonia [24]	€3,232
Direct and indirect cost of lifetime hearing aids as sequelae of meningitis [29]	€4,909
Direct and indirect cost of lifetime care as sequelae of meningitis [30]	€1,004,238
Direct and indirect cost of special education as sequelae of meningitis [30]	€176,259
Indirect cost (loss of production by parents) per episode of otitis media [9]	€136
Indirect cost (loss of production by parents) per case of pneumonia [9]	€136
Indirect cost (loss of production by parents) average per case of meningitis or bacteremia [9]	€291
Direct cost per case of invasive infection [20,24]	€6,303
Indirect cost per case of invasive infection [20,24]	€2,364
Friction cost per case of invasive infection [24]	€14,958
Proportion of cases of pneumonia that are mild [19]	0.750
Proportion of cases of pneumonia that are uncomplicated [19]	0.126
Proportion of cases of pneumonia that are complicated [19]	0.124
Proportion of meningitis survivors with hearing impairments that require lifetime hearing aids [29]	1.000
Proportion of meningitis survivors with neurological sequelae that require to be institutionalized for life [30]	0.250
Proportion of meningitis survivors with neurological sequelae that require lifetime special education [30]	0.500
Proportion of cases of meningitis that are complicated ^a [17]	0.400
Proportion of adult bacteremia cases that are serious ^a [17]	0.500
Proportion of cases pneumococcal meningitis with unilateral hearing impairment [31]	0.105
Proportion of cases pneumococcal meningitis with bilateral hearing impairment [31]	0.051
Proportion of cases pneumococcal meningitis with mental retardation [31]	0.042
Proportion of cases pneumococcal meningitis with spasticity [31]	0.035
Proportion of cases pneumococcal meningitis with epilepsy [31]	0.042

IPD, invasive pneumococcal disease.

^a Bos et al. conducted a expert panel meeting in 1999 with representatives of the pediatric departments of most academic hospitals in the Netherlands.

Table 3

Estimated mean and standard error for parameters used in the multivariate probabilistic sensitivity analysis with the appropriate references

Parameter description	Mean	SE
Vaccine efficacy against IPD at age 4–11 months—partially vaccinated individuals ^a [13]	0.857	0.2551
Vaccine efficacy against IPD after age 12 months—fully vaccinated individuals ^a [13]	0.939	0.0482
The effectiveness of the vaccine against episodes of otitis media (all causative agents) ^a [13]	0.064	0.0122
The effectiveness of the vaccine against clinical pneumonia (all causative agents) ^a [28]	0.06	0.0242
Reduction in total cases of IPD in unvaccinated age-group 20–39 ^a [16]	0.32	0.0408
Reduction in total cases of IPD in unvaccinated age-group 40–64 ^a [16]	0.08	0.0357
Reduction in total cases of IPD in unvaccinated age-group 65 and older ^a [16]	0.18	0.0332
Mortality of pneumococcal meningitis cases in children (population age mean 8 months) ^b [3]	0.169	0.0409
Mortality of pneumococcal bacteremia cases in children (population age < 15 years old) ^b [4]	0.06	0.0061
Mortality of pneumococcal meningitis cases in adults ^b [27]	0.304	0.0245
Mortality of bacteremia cases in adults ^b [26]	0.259	0.036
Serotype coverage of PCV7 of meningitis cases in the Netherlands ^b [21]	0.671	0.025
Serotype coverage of PCV9 of meningitis cases in the Netherlands ^b [21]	0.683	0.0247
Serotype coverage of PCV10 of meningitis cases in the Netherlands ^b [21]	0.782	0.0219
Serotype coverage of PCV13 of meningitis cases in the Netherlands ^b [21]	0.861	0.0184
Serotype coverage of PCV7 of bacteremia cases in the Netherlands ^b [21]	0.595	0.0256
Serotype coverage of PCV9 of bacteremia cases in the Netherlands ^b [21]	0.682	0.0243
Serotype coverage of PCV10 of bacteremia cases in the Netherlands ^b [21]	0.78	0.0216
Serotype coverage of PCV13 of bacteremia cases in the Netherlands ^b [21]	0.863	0.0179

For all parameters the standard beta distribution was used. IPD, invasive pneumococcal disease; PCV, pneumococcal conjugate vaccine + number of serotypes contained in vaccine; SE, standard error.

^a The standard error was calculated from values published in literature using Eq. (1) (see Box 1).^b The standard error was calculated from values published in literature using Eq. (2) (see Box 1).

Table 4

Average number of cases per year in the Netherlands of meningitis and bacteremia in unvaccinated age-groups over the years 2001–2004, caused by all serotypes of *Streptococcus pneumoniae*, corrected for underreporting [21] and estimated percentage of decline in the incidence of invasive pneumococcal disease for all serotypes in unvaccinated age groups according to Whitney et al. [16]

Age	Meningitis	Bacteremia	Decline incidence IPD (95% CI)
20–39 years	25	251	32 (23–39)
40–64 years	89	756	8 (1–15)
≥65 years	79	1493	18 (11–24)

Box 1: Equations used to derive the standard error from data commonly found in literature [32,34]

The distribution parameters are calculated by method of moments estimation. This requires an estimate of the mean and the standard error (SE). In case a proportion with a 95% confidence interval is available from the literature, the standard error can be approximated from the upper (u) and lower (l) limit of the interval with Eq. (1), assuming a normal distribution. If the data is published in the form of r 'successes' from n 'trials', as is often the case for mortality, Eq. (2) can be used to estimate the probability (\hat{p} , assumed as the mean) by maximum likelihood estimation and calculate the standard error, assuming a binomial sampling distribution [32].

$$SE \approx \frac{u - l}{2 \times 1.96} \quad (1)$$

$$SE = \sqrt{\frac{\hat{p}(1 - \hat{p})}{n}} \quad (2)$$

$$\hat{p} = \frac{r}{n}$$

error can be derived from data commonly published in literature. The results of a multivariate probabilistic sensitivity analysis are presented in a two-dimensional graph showing the acceptability curve and uncertainty interval for each selected outcome parameter. Optionally, a scatter plot can be generated showing the cost-effectiveness plane. Both estimates for the mean and median iCER are plotted in the graph. If possible, a 95% uncertainty interval is estimated and graphically shown by taking the 2.5 and 97.5 percentiles from the Monte Carlo simulations.

2.4. Scenario and sensitivity analysis

In addition to the base-case analysis, seven additional scenarios evaluating the impact of herd protection, the number of doses, the discount rate for effects, the number of serotypes in the vaccine and the duration of vaccine efficacy are presented. These scenarios are equal to the base-case scenario with the exception of the characteristics described in Table 5. Univariate sensitivity analysis was performed for the vaccine cost per dose and bivariate sensitivity analysis on the discount rate for costs and for effects. Multivariate probabilistic sensitivity analysis of second order uncertainty (1000 runs of Monte Carlo simulation) was performed using standard beta distributions [32]. Only parameters representing natural phenomena (efficacy, effectiveness, mortality, vaccine coverage and herd protection) were included in the multivariate analysis. Other parameters, such as unit costs were assumed to have a fixed value. All results and graphs presented in the results section were generated using the web interface.

3. Results

3.1. Base-case

In the base-case analysis the investment costs of the vaccination program would amount to €38,757,800, while it would prevent a total number of 78 deaths and 44 lifetime sequelae.

Table 5

Brief description of the seven alternative scenarios

Scenario	Description
No herd	A scenario assuming that no herd protection will occur.
3-doses	A scenario exploring the effects of a 3-doses instead of a 4-doses schedule. A change in the number of doses administered only affects the investment costs. It is assumed that this a scenario involves the same efficacy as the base-case analysis [15].
Low discount rate effects	A scenario applying a 1.5% instead of a 4% discount rate for health effects. It was anticipated that the Dutch guideline for pharmacoeconomic research, to discount both cost and health effects at 4%, might be changed to 4% for costs and 1.5% for health effects [24].
PCV9 ^a	Application of PCV9, a 9-valent vaccine that is currently under development by Wyeth, containing serotypes 1 and 5 in addition to the serotypes 4, 6B, 9V, 14, 18C, 19F, 23F contained in the 7-valent vaccine.
PCV10 ^a	Application of PCV10, a 10-valent vaccine that is currently under development by GSK and containing the serotypes of the 9-valent vaccine and 19A.
PCV13 ^a	Application of PCV13, a 13-valent vaccine that is currently under development by Wyeth, containing serotypes of the 10-valent vaccine and 3, 6A and 7F.
Effectiveness 5 years	A scenario that assumes the vaccine effectiveness lasts up to and including the age of 5 years.

^a A change in the number of serotypes affects the serotype coverage used to calculate vaccine effectiveness against IPD. It is assumed that this scenarios involves the same vaccine effectiveness as the base-case analysis.

Table 6

Health effects in the base-case analysis: discounted quality adjusted life years gained (QALYs), discounted life years gained (LYGs) and undiscounted cases averted for the vaccinated cohort, unvaccinated age groups and total

Life years	Vaccinees	Unvaccinated	Total
QALYs gained	529	868	1,397
LYGs	385	868	1,253
Cases averted	Vaccinees	Unvaccinated	Total
Meningitis	55	29	84
Bacteremia	103	205	308
Pneumonia	1,795		1,795
Otitis media	52,407		52,407
Lifetime sequelae	44		44
Death	16	62	78

Table 7

Cost averted (savings) in the base-case analysis (in €; price-levels: 2004) for the vaccinated cohort, unvaccinated age groups, and total

Direct costs averted	Vaccinees	Unvaccinated	Total
IPD	1,504,500	1,475,700	2,980,200
Non-invasive	1,998,000		1,998,000
Sequelae meningitis	6,077,600		6,077,600
Total	9,580,100	1,475,700	11,055,800
Indirect costs averted	Vaccinees	Unvaccinated	Total
IPD	43,100	553,500	596,600
IPD friction costs		926,900	926,900
Non-invasive	6,650,600		6,650,600
Total	6,693,700	1,480,400	8,174,100

lae, resulting in a total of 1397 discounted QALYs gained or 1253 discounted LYG. Averted direct and indirect costs (savings) would be €11,055,800 and €8,174,100, respectively. In the base-case analysis, the net costs of the program would therefore be €19,527,900, resulting in an iCER of the vaccination program at €14,000 per QALY or €15,600 per LYG. The cost-effectiveness threshold analysis estimated a vaccine cost per dose of €60.85. The detailed financial benefits and health effects of the vaccination program are presented in Tables 6 and 7. Results for the vaccinated cohort, unvaccinated age groups and totals are shown separately. In Table 8 the overall results are presented.

Table 9

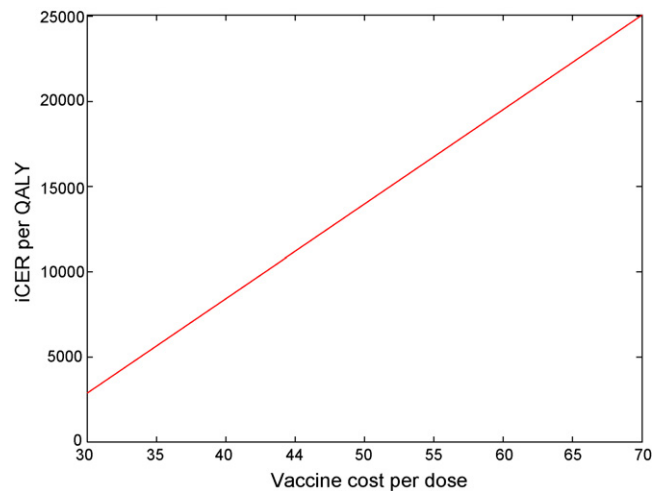
Mean incremental cost-effectiveness ratios (iCERs) per quality adjusted life year (QALY) gained and life year gained (LYG) with 95% uncertainty intervals (UI) derived from scatter plots for the base-case analysis and seven alternative scenarios (in €; price levels: 2004)

Scenario	iCER per QALY (95% UI)	iCER per LYG (95% UI)
Base-case	14,000 (9,800–20,200)	15,600 (10,800–22,800)
No herd	42,600 (31,300–72,800)	58,700 (40,500–103,600)
3-doses	7,000 (4,100–11,100)	7,800 (4,500–12,500)
Low discount rate effects	9,900 (7,000–13,900)	11,200 (7,800–16,000)
PCV9	13,000 (9,400–19,100)	14,700 (10,400–21,800)
PCV10	11,900 (8,600–17,200)	13,500 (9,500–19,800)
PCV13	10,400 (6,900–15,800)	11,900 (7,800–18,100)
Effectiveness 5 years	15,800 (11,500–22,700)	17,500 (12,500–25,400)

Table 8

Summary statistics on overall outcome in the base-case analysis (in €; price levels: 2004)

Measure	€
Investment costs	38,757,800
Direct savings	11,055,800
Indirect savings	8,174,100
Total savings	19,229,900
Net costs	19,527,900
iCER per QALY	14,000
iCER per LYG	15,600
Vaccine cost per dose at threshold	60.85

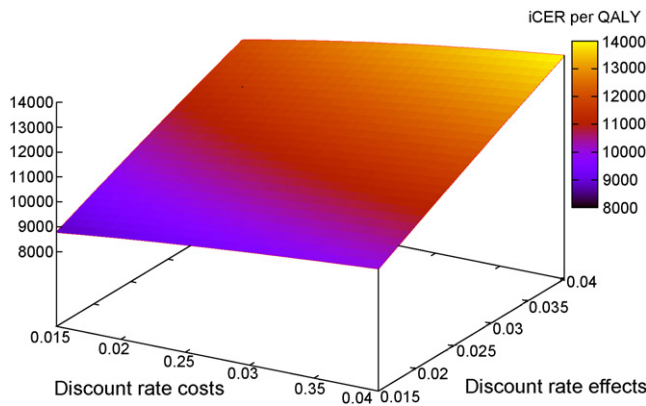


Graph 1. Univariate sensitivity analysis showing the effect on the iCER per QALY of varying the vaccine cost per dose from €30 to €70 (all other parameters as in the base-case analysis).

3.2. Scenario- and sensitivity analysis

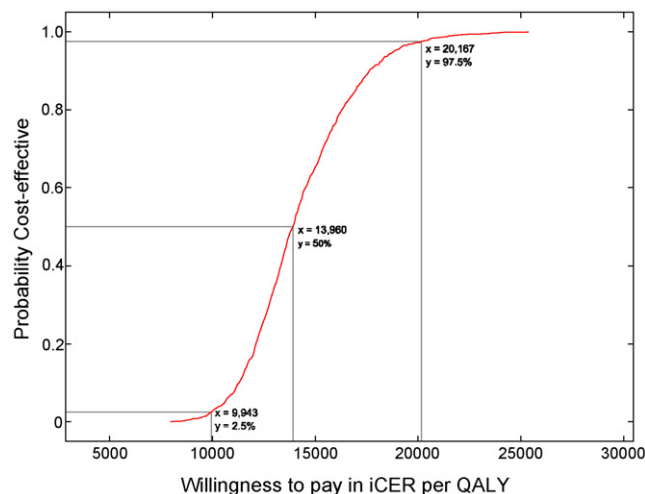
The results of the base-case and scenario analyses are presented in Table 9. Shown is the mean iCER per QALY and mean iCER per LYG, with their 95% uncertainty intervals estimated by multivariate probabilistic sensitivity analysis.

The results of the sensitivity analysis for the base-case analysis are presented in Graphs 1–4. The input parameters selected for sensitivity analysis that are presented here show the various functions of the web interface. Graph 1 shows the effect on the iCER per QALY of varying the vaccine cost per dose from €30–€70. A bivariate sensitivity analysis

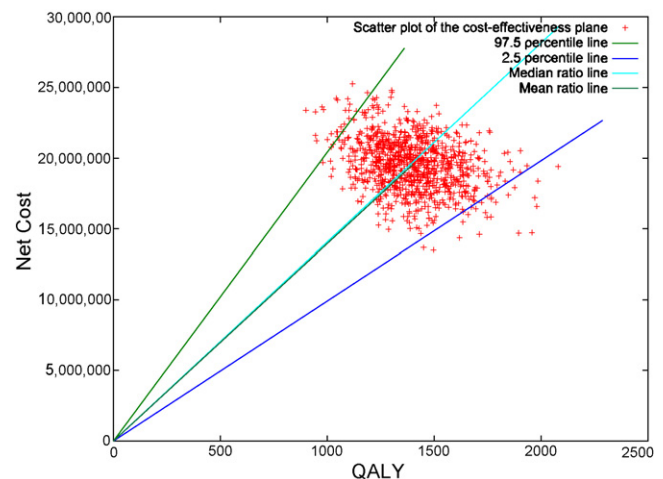


Graph 2. Bivariate sensitivity analysis showing the effect on the iCER per QALY of varying the discount rates for both costs and effects from 1.5% to 4% (all other parameters as in the base-case analysis).

is depicted in Graph 2, showing the effect on the iCER per QALY of varying the discount rates for costs and effects from 1.5% to 4%. The results of the multivariate probabilistic sensitivity analysis are displayed as an acceptability curve and as a scatter plot in Graphs 3 and 4, respectively. In Graph 3, the horizontal 2.5, 50 and 97.5 percentile lines are plotted representing the (rounded) median iCER of €14,000 with a 95% uncertainty interval of €9,900–20,200 per QALY. In Graph 4, the results are displayed as a scatter plot of the cost-effectiveness plane, with the health effects (here: QALYs gained) on the *x*-axis and the financial effects (net costs) on the *y*-axis. As explained above, further sensitivity analysis can be performed by the reader using the web interface of the model.



Graph 3. Results of the Monte Carlo simulation for the base-case analysis, presented as an acceptability curve of the iCER per QALY. Indicated are the horizontal 2.5, 50 and 97.5 percentile lines representing with corresponding vertical lines to the intercept values on the *x*-axis, representing a (rounded) median iCER of €14,000 with a 95% UI of €9,900–20,200 per QALY. A willingness to pay of €20,000 per QALY for the Netherlands corresponds to a high probability of being cost effective.



Graph 4. Results of the Monte Carlo simulation for the base-case analysis, presented as a scatter plot of the cost-effectiveness plane with 95% UI. This graph shows the health effects (here: QALYs gained) on the *x*-axis and the financial effects (net costs) on the *y*-axis. The 2.5, 50 and 97.5 percentile lines drawn, representing the UI lower bound, median and UI upper bound, respectively. Also drawn is the line representing the mean that in this case approximately coincides with the median.

4. Discussion

4.1. Study results

In 2001, the Dutch Ministry of Health decided not to include PCV7 in the NVP. This decision was based among other data on the conclusion from the results of the study by Bos et al. [17], that the cost-effectiveness ratio for inclusion of PCV7 in the NVP was unfavorable. Recent data on herd protection effects and a reduced dosage regimen have renewed the debate on inclusion of PCV7 in the NVP. Even with a slightly higher cost per dose of vaccination than previously analyzed, the results of our new study show a more favorable iCER of €14,000 per QALY or €15,600 per LYG compared to the previous estimates by Bos et al. of €71,250 per QALY or €82,700 per LYG. This difference can be largely attributed to the herd protection effects, as is illustrated by the iCER of €42,600 per QALY of scenario 'No herd', where herd protection effects are excluded. A smaller contribution to the lower iCER estimated in our study can be attributed to the use of vaccine coverages of PCV7 of 0.671 and 0.595 for pneumococcal meningitis and pneumococcal bacteremia, respectively, derived from more recent data [21]. Scenario 'No Herd', using a vaccine coverage of 0.58 and 0.52 as applied by Bos et al., results in an iCER of €51,200 per QALY. Also some difference is caused by various recent changes in the guidelines for costing in pharmacoeconomic research in the Netherlands [24]. In particular, the guideline costs of an inpatient day and those of production losses have increased significantly. Another factor of lesser importance is the use of different base years for costing (2001 versus 2004).

Ideally herd protection effects of PCV7 vaccination should be modeled using a dynamic transmission model, but cur-

rently data on the transmission dynamics of *Streptococcus pneumoniae* is only limited. To estimate the herd protection effects, data on the reduction of IPD in unvaccinated age groups in California have now been used. One important aspect in the occurrence of herd protection involves the contact patterns between age groups that could differ between the US and the Netherlands. Also, the herd protection effects did not include a decline in cases of otitis media and pneumonia in unvaccinated age groups due to unavailability of data. It is likely that this causes an underestimation of the beneficial health effects of the vaccine. Additionally, in our analysis it was assumed that serotype replacement is absent. However, recent evidence suggests that some serotype replacement may occur, implying that the beneficial health effects of the vaccine might be overestimated in our analysis. No data was available to estimate this effect, but at this moment we do not expect serotype-replacement to have a large impact on the estimated cost-effectiveness ratios [35].

Not surprisingly, the univariate sensitivity analysis shows that the iCER is highly sensitive for the vaccine cost per dose. The bivariate sensitivity analysis on discount rates very clearly illustrates that the iCER of the vaccination program is much more sensitive to the discount rate for effects than the rate for costs. This is a general phenomenon for economic evaluations of infant vaccination programs, and often for any preventive program [36]. The results of the probabilistic sensitivity analysis, as shown in Graph 3, indicate that at a willingness to pay of 20,000 per QALY for the Netherlands [25] the inclusion of PCV7 in the NVP of the Netherlands can be considered cost effective with a high probability.

4.2. Web interface

To enhance the transparency of economic evaluation and provide the decision maker with an instrument to ensure a minimum quality of such analyses, guidelines for pharmacoeconomic research have been formulated for a growing number of countries (<http://www.ispor.org/PEguidelines/index.asp>). These guidelines include recommendations on good modeling practice, including for example checks to ensure internal and external validity, transparency and study design. Any evaluation of a vaccine should adhere to these general guidelines for health economics [37]. As such, these guidelines – and adherence to it – in combination with peer-reviewed publication of the model, should guarantee a minimum level of quality allowing the decision maker to base a decision on the (published) results.

However, these guidelines do not address all specific problems remaining in economic evaluation of (new) vaccines. In this study we focus on the limitations of the flexibility and transparency inherent in the manner economic evaluations are published. On flexibility, firstly, we note that after publication additional information from (observational) studies may become available, e.g. on effectiveness and serotype coverage of the vaccine of interest. As this type of economic evaluation is often performed in the pre-marketing period, the

model parameters are primarily based on the results of a limited number of trials, some of which might be still ongoing. Therefore, the evidence available at the time of submission is likely to change.

Secondly, the decision maker's demand for information may change over time and although the model on which an evaluation was based may still be relevant, the published results alone may not suffice. The decision maker may require updates of the published analyses or additional scenarios to be investigated that may address various what-if scenarios to better appreciate all political factors involved. Given the potential difference in interests and sub-optimal communication between decision makers and researchers, it is unrealistic to expect that the author(s) can anticipate all relevant scenarios. Moreover, published scenario- and sensitivity analyses are limited by the obvious practical constraints of a journal and the choices made by the author(s). In addition, it is not practical nor accepted by journals to publish updates of evaluations over short intervals of time whenever the decision maker's information need changes, or new evidence becomes available.

An important issue regarding transparency is that decision makers often perceive economic studies as incomprehensible 'black boxes', because the model is not fully published and usually not integrally part of the peer-review process. By providing more clarity as recommended by Beutels [38], a web interface might help to remove this bias to some extent. By performing sensitivity analysis on the model the user is provided with additional understanding of the limitations of the model, while information about the uncertainty of the model parameters is obtained by observing the impact of changes in model parameters. Also, the ability to perform sensitivity and scenario analysis on all relevant model parameters facilitates the assessment of international transferability and may help adaptation of the study design to other geographical areas if desired [39]. Users can study the model behavior in more detail, test its robustness and adapt the model to their local conditions to assess its validity. Interaction with the economic model through a web interface might also allow a more thorough peer-review of the model prior to publication.

Ideally, the decision maker or user should be able to "play around" with a user-friendly and validated model to compare different conditions of vaccine application and payment. We believe that the usability of economic evaluations of vaccines could be improved by making the models of economic evaluations available on the Internet, parallel with the peer-reviewed publication in the scientific literature.

One of the limitations of the interactive model is that it does not allow the user to adjust the model to allow for effects that require structural changes. Also, the number of runs in the Monte Carlo simulation used in multivariate sensitivity analysis is limited to 1000 to reduce the load on the server. In addition, extending the user interface with options for advanced sensitivity analysis increases complexity that might limit the usability for decision makers.

5. Conclusions

We have demonstrated the application of a web interface to allow interaction with a cost-effectiveness model for PCV7. We have suggested the potential benefits of making models of economic evaluations available in this way parallel with a publication in a journal, to enhance decision support and improve flexibility and transparency. Our approach was exemplified with a model projecting the impact of nation-wide infant vaccination with PCV7 in the Netherlands. For this analysis, the iCER per QALY, estimated by our analysis of the base-case scenario, is 14,000 (95% UI: 9,800–20,200). At a willingness to pay of 20,000 per QALY for the Netherlands [25] the PCV7 vaccination program can be considered cost effective with a high probability. The substantial difference with the base-case iCER per QALY of 71,250 reported by Bos et al. [17] can for the greater part be attributed to the inclusion of the effects of herd protection in the model. To our knowledge, this is the first economic evaluation of a vaccination program that describes the use of a web interface to bridge the gap between analyst and decision maker. The usefulness of this approach will have to be confirmed by use in practice.

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